CHAPTER II

ESSAY

Cost-effectiveness of the treatment of latent tuberculosis infection to HIV-infected person

2.1 Introduction

The interaction between tuberculosis and HIV has implications for the public health approach to tuberculosis control among HIV-infected people. Untreated HIV infection leads to progressive immunodeficiency and increased susceptibility to infections, including promotes progression to active tuberculosis in people with recently acquired and with latent *M tuberculosis* infection. Tuberculosis in high HIV prevalence populations is a leading cause of morbidity and mortality, and HIV is driving the tuberculosis epidemic in many countries. Tuberculosis programmes and HIV programmes therefore share mutual concerns: prevention of HIV should be a priority for tuberculosis control; tuberculosis care and prevention should be priority concerns of HIV/AIDS programmes.

The efforts to control tuberculosis among HIV-infected people have mainly focused on implementing the DOTS strategy for tuberculosis control, i.e. identifying

and curing tuberculosis disease cases. The expanded scope of the new strategy for tuberculosis control in high HIV prevalence populations comprises interventions against tuberculosis (intensified case-finding and cure and **tuberculosis preventive treatment**) and interventions against HIV (and therefore indirectly against tuberculosis), e.g. condoms, STI treatment, safe injecting drug use (IDU) and highly active antiretroviral treatment (HAART).

However, In the world, we have limited of resources such as people, time, facilities, equipment and knowledge. Therefore choices must be made so that these scare resource are used to maximized the efficiency and effectiveness of the program especially Thailand that facing with economic crisis. Therefore, if the policy maker want to make decision for any program, service, health procedure and intervention, the systematic analysis is needed to identify clearly the relevant alternative with economic evaluation.

2.2 HIV epidemiology

Twenty years after the first clinical evidence of acquired immunodeficiency syndrome was reported, AIDS has become the most devastating disease humankind has ever faced.

2.2.1 Global HIV epidemiology

At the end of 2001, WHO and Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated 40 million people globally were living with HIV. In many parts of the developing world, the majority of new infections occur in young adults, with young women especially vulnerable. About one-third of those currently living with HIV/AIDS are aged 15–24. Most of them do not know they carry the virus. Many millions more know nothing or too little about HIV to protect themselves against it. Of the global total of 40 million people living with HIV/AIDS (PLWH) at the end of 2001, 28.1 million (70.25%) are in sub-Saharan Africa and 7.1 million (17.75%) are in South East Asia. Sub-Saharan Africa thus bears the largest burden of the HIV/AIDS epidemic without adequate treatment and care. In South East Asia , the apparently low national prevalence rates in many countries in this region are dangerously deceptive. They hide localized epidemics in different areas, including some of the world's most populous countries. There is a serious threat of major, generalized epidemics. But, as Cambodia and Thailand have shown, prompt, large-scale prevention programmes can hold the epidemic at bay. [WHO&UNAIDS, 2001]

2.2.2 HIV/AIDS situation in Thailand

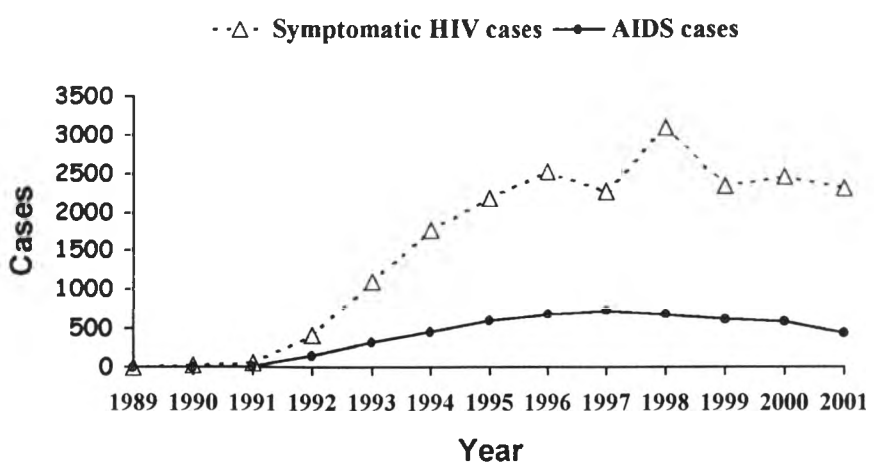
Thailand is experiencing one of Asis's most severe AIDS crises. The first cases of AIDS were reported in 1984-a man returning from overseas and receiving treatment in a Bangkok hospital.[Phanupak et al., 1985] As of the end of 2001, it was estimated that approximately 665,000 adults and Children were living with HIV/AIDS in

Thailand. In 2001, 55,009 adults and children died of AIDS. Cumulative reported AIDS cases through December 2001(185,907) demonstrate that sexual transmission accounts for the majority of cased(83.3%). [Thailand MOPH&CDC-US 2002]

2.2.3 HIV/AIDS situation in Chiang Rai

The first HIV case in Chiang Rai was reported in 1988 [Division of Epidemiology, 1989] In 1990, the data from the HIV sero-sentinel surveilance in this province showed increasing prevalence of HIV/AIDS but have trend to decrease.(See figure 2.1)

Figure 2.1 Cases of AIDS and symptomatic HIV infection in Chiang Rai, 1989-2001



Source: Chiang Rai Provincial Health Office, 2001

2.3 TB epimediology

About a century after Koch's discovery of *M. tuberculosis* bacilli the tuberculosis epidemic which had appeared under control was again recognized as a major global health threat [Hochi, 1994]

2.3.1 Global TB epimediology

The global epidemic is growing and becoming more dangerous. The breakdown in health services, the spread of HIV/AIDS and the emergence of multidrug-resistant TB are contributing to the worsening impact of this disease. Each year, more people are dying of TB. New outbreaks have occurred in Eastern Europe, where TB deaths are increasing after almost 40 years of steady decline. In terms of numbers of cases, the biggest burden of TB is in south-east Asia. [WHO, 2001]

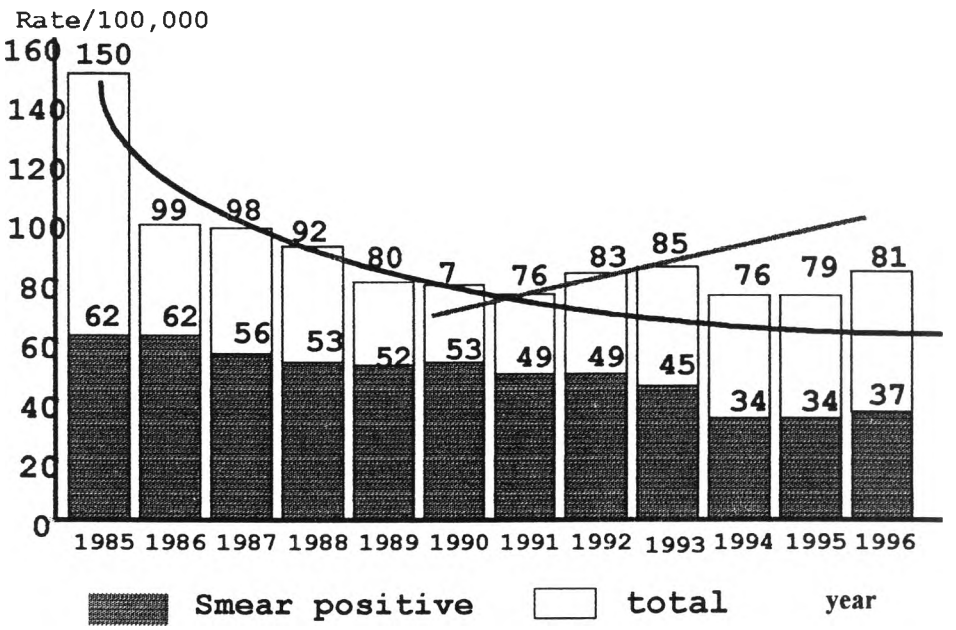
- TB kills about 2 million people each year.
- Around 8 million people become sick with TB each year.
- Over 1.5 million TB cases per year occur in sub-Saharan Africa. This number is rising rapidly as a result of the HIV/AIDS epidemic.
- Nearly 3 million TB cases per year occur in south-east Asia.
- Over a quarter of a million TB cases per year occur in Eastern Europe.

2.3.2 TB situation in Thailand

Thailand has experienced a continuous decline of tuberculosis epidemic in the decades following the second world war. The tuberculosis National prevalence survey was conducted in 1962,1977 and 1991. The sputum examination were used to calculate the tuberculosis prevalence as result; TB rate for all age groups was 500 cases per 100,000 population in 1962, 300 cases per 100,000 population in 1977 and 230 cases per 100,000 population in 1991. [Payanandana et al., 1992]

Continuous reports of notified cases are available since 1980. The highest reported incidence rate of 150 cases per 100,000 population was observed in 1985, whereafter the rate declined to 76 cases per 100,000 population in 1991 [CDC Ministry of Public Health Thailand & WHO, 1999] due mainly to implementation of short course regimens and improved therapeutic coverage and efficacy. With this performance of the National Tuberculosis Program (NTP) and national economical and social development, Thailand had a steady decline in tuberculosis from that of highly endemic area to that of a moderate endemic area (See in figure 2.2) as shown before the HIV epidemic era. But, it appeared to revert to a new trend of increasing new TB cases during 1992-1997 due to the impact of the HIV epidemic.

Figure 2.2 Rate per 100,000 of new TB cases, Thailand 1985-1996

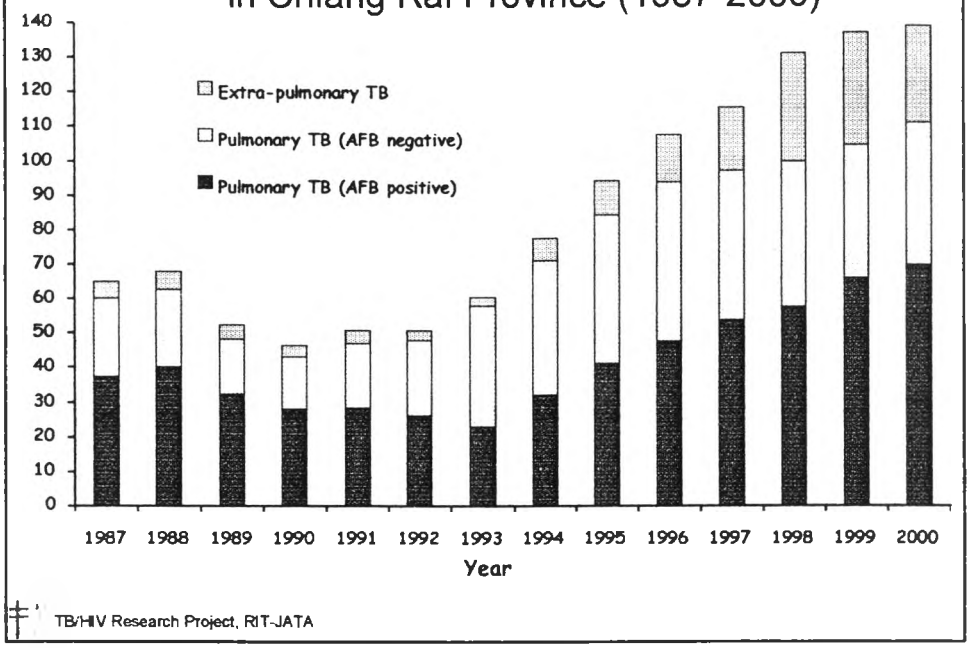


Source: Tuberculosis Division, Ministry of Public Health Thailand

2.3.3 TB situation in Chiang Rai Province

A population-based surveillance study was set up in Chiang Rai province, the northern Thailand. The incidence rates of new TB per 100,000 population were 50 in 1990 and 63 in 1997 and increase to 117 in 1998 and 140 in 999. [Saisorn et al., 1999] (See in figure 2.3) To effectively cope with the increasing TB burden, improvement of TB services by Directly Observed Therapy- Short Course (DOTS) was started in pilot district in 1996. DOTS is an effective strategy to control TB and advocated by World Health Organization.

Figure 2.3: New TB rate per 100,000 persons in Chiang Rai Province (1987-2000)



2.4 Global TB/HIV epidemiology

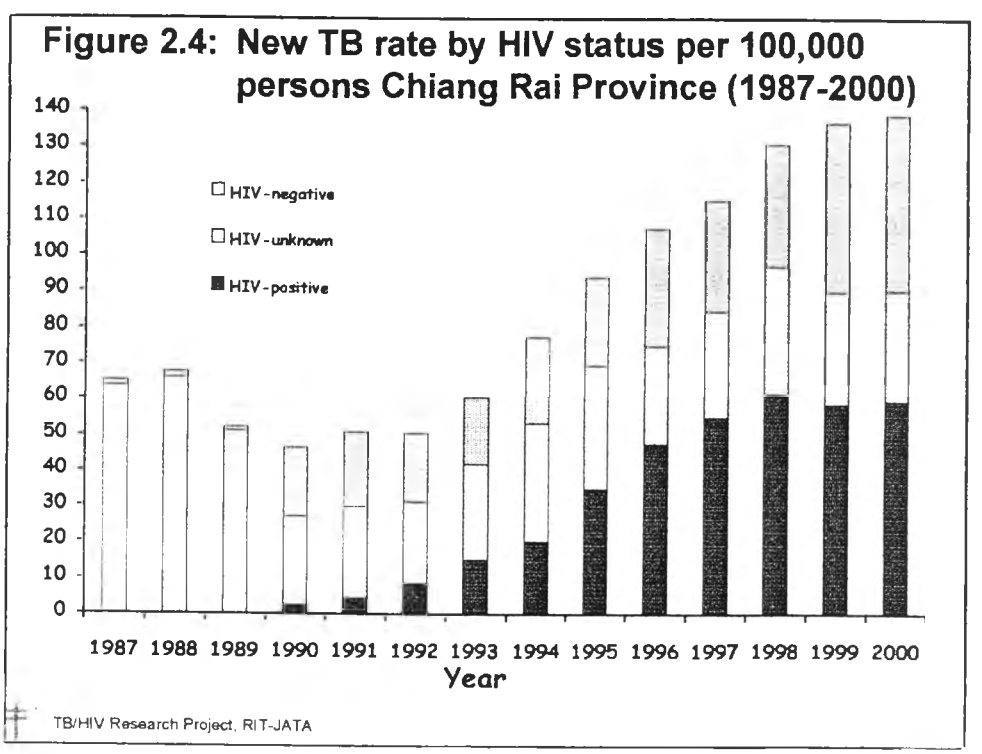
HIV and TB are closely linked. Testing in a number of developing countries shows that up to 70% of TB patients are infected with HIV. In addition, up to 50% of people living with HIV can expect to develop TB. Worldwide, 36.1 million people are infected with HIV at the end of 2000 and 95% of them live in developing countries, where TB rates are highest. About a third of the 36.1 million PLWH (13 million people) are infected with both HIV and the germ that causes TB.

Since 68% of those co-infected live in sub-Saharan Africa and with 22% of those co-infected live in South East Asia.[WHO/UNAIDS 2001] People with both diseases suffer double discrimination

2.5 TB/HIV epidemiology in Thailand and Chiang Rai province

At the national level, the HIV prevalence among TB patients increased from 3.1% in 1989 to a peak of 18.9 % in 1996 before decreasing to 16.8 % and 15.8% in 1997 and 1998 respectively. The co-infection of TB/HIV is difference in each region. In upper northern region, the HIV prevalence among TB patients increased from 5.4% in 1989 to 45.7% in 1995 and has been stable at between 30-40%. However, the other region also increased but has not exceeded 30%.[Payanandana et al., 1999]

In Chiang Rai province, as mention that the incidence rates of new TB are still increase in spite of the recent decline in HIV incidence and prevalence, HIV still has long-term impacts on tuberculosis. Among TB patients, the HIV prevalence increased from 2.33% (24.3% unknown , 19.32 % HIV-negative) in 1990 to 59.60%(30.7% unknown , 48.51 % HIV-negative) and 32% HIV were negative and 25% were unknown (See in figure2.4)



2.6 Impact of HIV on tuberculosis

HIV fuels the tuberculosis epidemic in several ways. HIV promotes progression to active tuberculosis both in people with recently acquired [DiPerri et al., 1989] and with latent *M tuberculosis* infections. [Raviglione et al., 1997] HIV is the most powerful known risk factor for reactivation of latent tuberculosis infection to active disease. [Rieder et al., 1989] The annual risk of developing tuberculosis in a PLWH who is co-infected with *M. tuberculosis* ranges from 5-15%.[Raviglione et al., 1997] HIV increases the rate of recurrent tuberculosis, [Fitzgerald et al. 2000] which may be due to either endogenous reactivation (true relapse) or exogenous re-infection. [Daley et al., 1993] Increasing tuberculosis cases in PLWH pose an increased risk of tuberculosis transmission to the general community, whether or not HIV-infected.

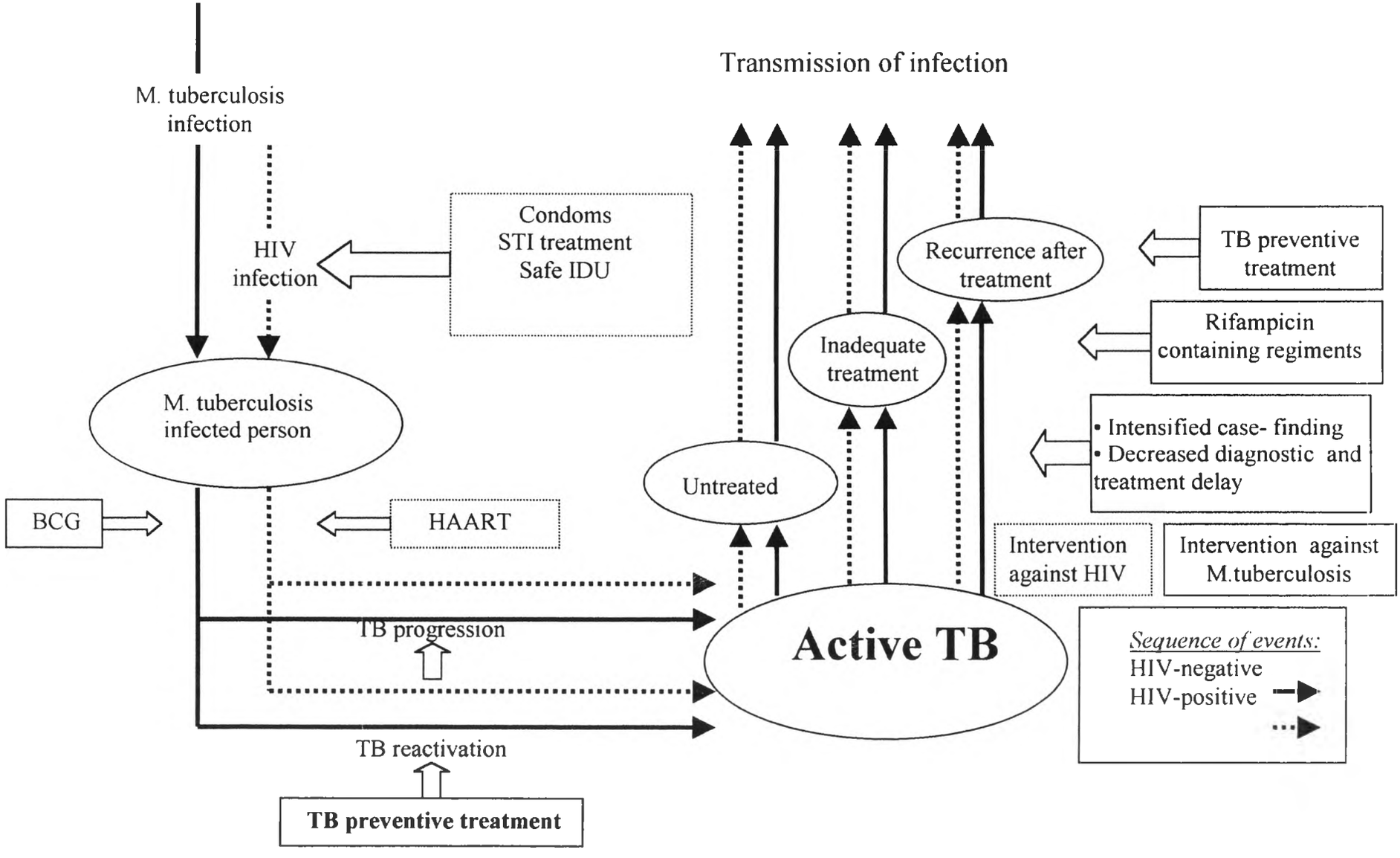
Therefore, the intervention for TB control program is a strong needed and also HIV control program.

2.7 Interventions to control tuberculosis in high HIV prevalence

The interaction between tuberculosis and HIV has implications for the public health approach to tuberculosis control among HIV-infected people. The expanded scope of the new strategy for tuberculosis control in high HIV prevalence populations comprises: (See in figure 5)

- **Indirectly against tuberculosis**: interventions against HIV
- **Directly against tuberculosis**: intensified tuberculosis case-finding and cure; tuberculosis preventive treatment; BCG vaccination and environmental tuberculosis control.

Figure 2.5 Interventions to interrupt the sequence of events by which HIV fuels TB epidemic



2.7.1 Interventions indirectly against tuberculosis (Intervention against HIV)

prevention of HIV should be a priority for tuberculosis control and also tuberculosis care and prevention should be priority concerns of HIV/AIDS programmes.

2.7.1.1 Interventions to decrease HIV transmission

Since HIV fuels the tuberculosis epidemic, interventions to decrease HIV transmission should contribute to decreasing the tuberculosis burden. Increased condom use, treatment of STIs, reduction in the number of sexual partners, safe injecting behavior, and drugs to prevent mother-to-child transmission have all been shown effective in preventing HIV infection in pilot projects, controlled trials, or national programmes in less-developed countries.[Merson et al., 2000]

2.7.1.2 Antiretroviral therapy

There is a need to evaluate whether combination antiretroviral (ARV) therapy in high HIV prevalence populations in sub-Saharan Africa has the same impact in reducing (or postponing) the incidence of tuberculosis as has been shown in the USA [Jones et al., 2000], Brazil [Chequer et al., 2000] , and Italy [Girardi et al., 2000]

2.7.2 Interventions directly against tuberculosis

The burden of illness revealed an urgent need for intervention. Possible interventions for the prevention of the tuberculosis burden are summarized below:

2.7.2.1 Tuberculosis case-finding and treatment to ensure cure

Case-finding and treatment to ensure cure are the core tuberculosis control activities. In terms of communicable disease control, the aim is to reduce the average number of people infected by each infectious case sufficiently to interrupt transmission. In order to offset the adverse effect of HIV on the tuberculosis epidemic, [Lienhardt et al. 1997] tuberculosis control programmes have to be more effective in diagnosing more infectious cases earlier and maximizing achievable treatment success rates in order to interrupt transmission. The most efficient approach to detecting more cases and with shortened duration of infectivity involves intensified case-finding in settings where HIV-infected people are concentrated.

2.7.2.2 BCG immunization

BCG has little or no effect in reducing the number of adult cases of infectious pulmonary tuberculosis, and so has limited impact on tuberculosis control. [WHO, 1995]

2.7.2.3 Preventive tuberculosis treatment

Preventive tuberculosis treatment may be aimed as following: [WHO, 2002]

a) Aimed at decreasing the risk of a first ever episode of tuberculosis

People at high risk of developing tuberculosis may benefit from preventive treatment, as an intervention currently for individual benefit rather than as a public health measure to control tuberculosis.

b) Aimed at decreasing risk of a recurrent episode of tuberculosis

Studies in the former Zaire [Perriens et al. 1995] and in Haiti [Fitzgerald et al. 2000] showed a higher rate of recurrent tuberculosis in HIV-infected individuals than in non-HIV-infected individuals treated with a 6-month regimen containing rifampicin throughout (the regimen used in the study in Zaire had a 4-drug initial phase and that in Haiti had a 3-drug initial phase). In both studies, post-treatment prophylaxis (isoniazid and rifampicin in the study in Zaire and isoniazid in the study in Haiti) decreased the risk of tuberculosis recurrence in HIV-infected individuals, but did not prolong survival.

However, the preventive tuberculosis treatment **(Treatment of latent tuberculosis infection)** which have several key point that needed understanding as following:

2.8 What is latent TB infection?

Latent Tuberculosis Infection(LTBI) : According to Self-Study Modules on Tuberculosis means that tubercle bacilli are in the body but the immune system is keeping them under control. In most people who breathe in TB bacteria and become infected, the body is able to fight the bacteria to stop them from growing. The bacteria become inactive, but they remain alive in the body and can become active later. People with latent TB infection have characteristics as following:

- have no symptoms
- don't feel sick
- can't spread TB to others
- usually have a positive skin test reaction

Many people who have latent TB infection never develop TB disease. In these people, the TB bacteria remain inactive for a lifetime without causing disease. But in other people, especially people who have weak immune systems, the bacteria become active and cause TB disease. People who have LTBI but not TB disease are not infectious, in the other word, they cannot spread the infection to other people. These people usually have a normal chest x-ray. It is important to remember that TB infection is not considered a case of TB. Major similarities and differences between TB infection and TB disease are shown in Table 2.1[Self-study Modules on Tuberculosis, CDC-US]

Table 2.1 : TB Infection vs. TB Disease

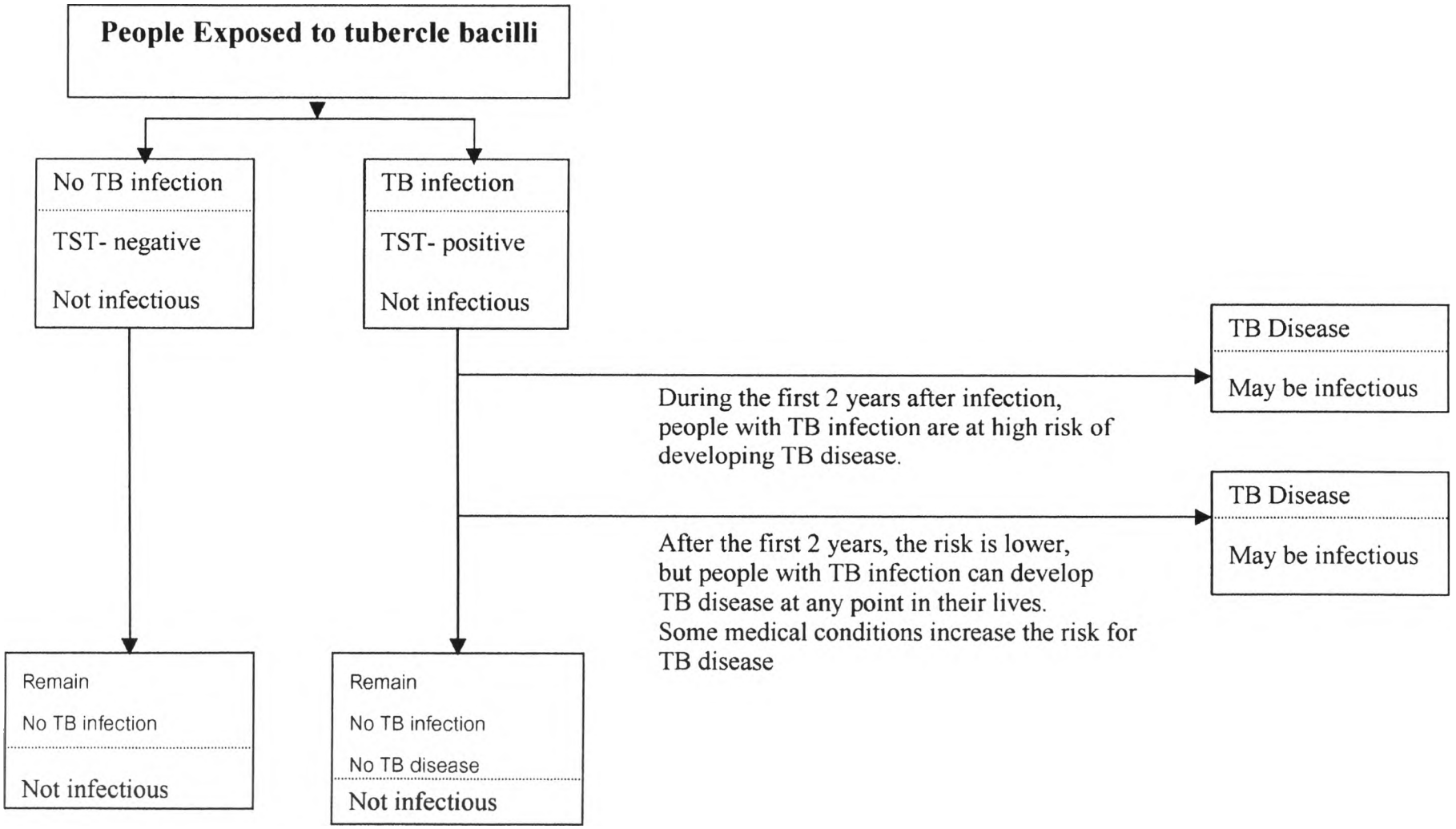
TB Infection	TB Disease (in the lungs)
Tubercle bacilli in the body	Tubercle bacilli in the body
Tuberculin skin test reaction usually **positive**	Tuberculin skin test reaction usually **positive**
Chest x-ray usually **normal**	Chest x-ray usually **abnormal**
Sputum smears and cultures **negative**	Sputum smears and cultures **positive**
No symptoms	**Symptoms** such as cough, fever, weight loss
Not infectious	**Often infectious** before treatment
Not a case of TB	**A case** of TB

Source: Centers for Disease Control & Prevention, National Center for HIV, STD, and TB Prevention, Division of Tuberculosis Elimination, Self-Study Modules on Tuberculosis

2.9 What is TB disease?

Some people with TB infection develop TB disease. TB disease develops when the immune system cannot keep the tubercle bacilli under control and the bacilli begin to multiply rapidly in the body and cause TB disease. The risk that TB disease will develop is higher for some people than for others. TB disease can develop very soon after infection or many years after infection. In the United States, about 5% of the people who have recently been infected with *M. tuberculosis* will develop TB disease in the first year or two after infection. Another 5% will develop disease later in their lives. In other words, **about 10% of all people who have TB infection will develop disease at some point**. The remaining 90% will stay infected, but free of disease, for the rest of their lives as this figure2.6

Figure 2.6: Progression of TB



2.10 Risk factors of people with TB infection develop to TB disease

Some conditions appear to increase the risk that TB infection will progress to disease (Table 2.2). The risk may be about 3 times higher (as with diabetes) to more than 100 times higher (as with HIV infection).

Table 2.2 : Risk Factors for the Development of TB Disease

Risk Factor	**How Many Times Higher Is the Risk of TB Disease?[1]**
Acquired immunodeficiency syndrome (AIDS)	170
HIV infection	113
Recent TB infection (within past 2 years)	15
Certain medical conditions[2]	3-16

1 Compared to the risk for people with no known risk factors

2 For example, diabetes, certain types of cancer, or immunosuppressive therapy

And also including some of these conditions is high risk for developing TB disease as following:

- babies and young children
- people who inject drugs
- people who are sick with other diseases that weaken the immune system (cancer, diabetes mellitus, silicosis)
- Immunosuppressive therapy

- Low body weight(10% or more below ideal)
- elderly people

If I have latent TB infection, how can I keep from developing TB disease?

Many people who have latent TB infection never develop TB disease. But some people who have latent TB infection are more likely to develop TB disease than others. If you have latent TB infection (a positive skin test reaction) and you are in one of these high-risk groups, you need to take medicine to keep from developing TB disease. This is called **treatment of latent TB infection.**

2.11 What is treatment of latent TB infection?

Treatment for latent TB infection (Preventive therapy) is the use of medication one or more anti-tuberculous drug given to people who have *Mycobacterium tuberculosis* infection in order to prevent the progression to TB disease. [WHO/UNAIDS, 1999]

2.12 Who is the target group of treatment of latent TB infection?

People in these groups should receive high priority for preventive therapy if they have a positive tuberculin skin test reaction (See in table 2.3) [Self-study modules on Tuberculosis , CDC-US]

Table 2.3 : High-Priority Candidates for Preventive Therapy

People in these groups should be given high priority for preventive therapy if they have a positive skin test reaction[1] **regardless of their age:**	People in the these groups should be given high priority for preventive therapy if they have a positive skin test reaction[1] and they are **younger than 35:**
# People with HIV infection[2] # Close contacts of people with infectious TB disease[2] # People whose skin test reaction converted from negative to positive within the past 2 years # People with chest x-ray findings suggestive of previous TB disease # People who inject illicit drugs # People with medical conditions that appear to increase the risk for TB disease (see Module 1, Transmission and Pathogenesis of Tuberculosis)	# People born in areas of the world where TB is common (for example, Asia, Africa, or Latin America) # Low-income groups with poor access to health care # People who live in residential facilities (for example, nursing homes or correctional facilities) # Children younger than 4 years old # People in other groups as identified by local public health officials

1 positive skin test reaction= An induration of 5 or more millimeters is considered positive for PLWA, close contacts, drug user with unknown HIV status.
An induration of 10 or more millimeters is considered positive for IDU-HIV negative,people with certain medical conditions.
An induration of 15 or more millimeters is considered positive for people with no risk factors for TB.

2 In certain circumstances, people in these categories may be given preventive therapy even if they do not have a positive tuberculin skin test reaction.

What if I have HIV infection?

A person can have latent TB infection for years without any signs of disease. But if that person's immune system gets weak, the infection can quickly turn into TB disease. Also, if a person who has a weak immune system spends time with someone with infectious TB, he or she may become infected with TB bacteria and quickly develop TB disease. Because HIV infection weakens the immune system, people with latent TB infection and HIV infection are at very high risk of developing TB disease. All HIV-infected people should be given a TB skin test to find out if they have latent TB infection. If they have latent TB infection, they need treatment for latent TB infection as soon as possible to prevent them from developing TB disease. If they have TB disease, they must take medicine to cure the disease. TB disease can be prevented and cured, even in people with HIV infection.

2.13 Treatment regimens of Latent Tuberculosis Infection

(U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES, Centers for Disease Control and Prevention (CDC) Atlanta, 2000)

Recommended regimens.

Four regimens are recommended for the treatment of adults with LTBI (See table 2.4)

Table 2.4 Recommended drug regimens for treatment of latent tuberculosis infection in adults

Drug	Interval and duration	Comments	Rating* (Evidence)† HIV⁻	HIV⁺
Isoniazid	Daily for 9 mo‡,§	In human immunodeficiency virus (HIV)-infected patients, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs)	A (II)	A (II)
	Twice weekly for 9 mo‡,§	Directly observed therapy (DOT) must be used with twice-weekly dosing	B (II)	B (II)
Isoniazid	Daily for 6 mo§	Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children	B (I)	C (I)
	Twice weekly for 6 mo§	DOT must be used with twice-weekly dosing	B (II)	C (I)
Rifampin plus pyrazinamide	Daily for 2 mo	May also be offered to persons who are contacts of pyrazinamide patients with isoniazid-resistant, rifampin-susceptible TB	B (II)	A (I)
		In HIV-infected patients, protease inhibitors or NNRTIs should generally not be administered concurrently with rifampin; rifabutin can be used as an alternative for patients treated with indinavir, nelfinavir, amprenivir, ritonavir, or efavirenz, and possibly with nevirapine or soft-gel saquinavir¶		
	Twice weekly for 2–3 mo	DOT must be used with twice-weekly dosing	C (II)	C (I)
Rifampin	Daily for 4 mo	For persons who cannot tolerate pyrazinamide	B (II)	B (III)
		For persons who are contacts of patients with isoniazid-resistant, rifampin-susceptible TB who cannot tolerate pyrazinamide		

* Strength of recommendation: A=preferred; B=acceptable alternative; C=offer when A and B cannot be given.

† Quality of evidence: I=randomized clinical trial data; II=data from clinical trials that are not randomized or were conducted in other populations; III=expert opinion.

‡ Recommended regimen for children younger than 18 yr of age.

§ Recommended regimens for pregnant women. Some experts would use rifampin and pyrazinamide for 2 mo as an alternative regimen in HIV-infected pregnant women, although pyrazinamide should be avoided during the first trimester.

¶ Rifabutin should not be used with hard-gel saquinavir or delavirdine. When used with other protease inhibitors or NNRTIs, dose adjustment of rifabutin may be required (see Table 8).

2.13.1 Isoniazid for 9 months.

The isoniazid daily regimen for 9 mo receives an A recommendation. Prospective, randomized trials of up to 12 mo of therapy in HIV-uninfected persons suggest that the maximal beneficial effect of isoniazid is achieved by 9 mo; minimal additional benefit is gained by extending treatment to 12 mo. Thus, this updated recommendation represents a shortening of the previous recommendation of isoniazid daily for 12 mo for HIV-infected persons and a lengthening of the previously recommended 6 mo for HIV-uninfected persons [American Thoracic Society, Centers for Disease Control. 1994] Both 12-mo and 6-mo regimens of isoniazid have substantially reduced rates of TB in HIV-infected persons compared with placebo [Bucher et al.1999] but the 6-mo regimen has not been directly compared with the 12-mo regimen in HIV-infected persons. Thus, the recommendation for 9 mo of isoniazid in HIV-infected persons is based on extrapolation of available data. Intermittent dosing of 9 mo of isoniazid for treatment of LTBI has not been studied comparatively. However, analogous with the continuation phase of treatment for active TB (where twice-weekly dosing is equivalent to daily dosing), twice-weekly dosing of isoniazid is also acceptable for treatment of LTBI, but is recommended at the B level as an acceptable alternative regimen.

2.13.2 Rifampin and pyrazinamide for 2 months.

The 2-mo daily regimen of rifampin and pyrazinamide is recommended on the basis of a prospective randomized trial of treatment of LTBI in HIV-infected persons

that demonstrated the 2-mo regimen to be similar in safety and efficacy to a 12-mo regimen of isoniazid [Gordin et al. 2000] Although this regimen has not been evaluated in HIV-uninfected persons with LTBI, the efficacy is not expected to differ significantly. However, the toxicities may be increased [Geiter. 1997] ; therefore, the recommendation is made at the A level for HIV-infected persons and at the B level for HIVuninfected persons until further data are available. Two randomized, prospective trials of intermittent dosing of rifampin and pyrazinamide for 2 and 3 mo, respectively, have been reported in HIV-infected persons [Mwinga et al. 1998, Halsey et al. 1998] ; in neither case was the sample size adequate to conclude with certainty that efficacy was equivalent to daily dosing. Moreover, both studies compared the twice-weekly rifampin and pyrazinamide regimen to the 6-mo isoniazid regimen. Therefore, rifampin and pyrazinamide given twice weekly for 2–3 mo may be considered when alternative regimens cannot be given. This recommendation is made at the C level.

2.13.3 Drug toxicity of treatment regimens

The antituberculosis medications used in these regimens have varying doses, toxicity, and monitoring requirements (See table 2.5). [CDC-US, 2000]

Table 2.5 Medications to treat tuberculosis infection: Doses, toxicity, and monitoring requirements

Drug	Oral dose (mg/kg) (maximum dose)				Adverse reactions	Monitoring	Comments
	Daily		Twice weekly*				
	Adults	Children	Adults	Children			
Isoniazid	5 (300 mg)	10–20 (300 mg)	15 (900 mg)	20–40 (900 mg)	Rash Hepatic enzyme elevation Hepatitis Peripheral neuropathy Mild central nervous system effects Drug interactions resulting in increased phenytoin (Dilantin) or Disulfiram (Antabuse) levels	Clinical monitoring monthly Liver function tests† at baseline in selected cases‡ and repeat measurements if: Baseline results are abnormal Patient is pregnant, in the immediate postpartum period, or at high risk for adverse reactions Patient has symptoms of adverse reactions	Hepatitis risk increases with age and alcohol consumption Pyridoxine (vitamin B_6, 10–25 mg/d) might prevent peripheral neurophathy and central nervous system effects
Rifampin	10 (600 mg)	10–20 (600 mg)	10 (600 mg)	—	Rash Hepatitis Fever Thrombocytopenia Flu-like symptoms Orange-colored body fluids (secretions, urine, tears)	Clinical monitoring at weeks 2, 4, and 8 when pyrazinamide given Complete blood count, platelets, and liver function tests† at baseline in selected cases‡ and repeat measurements if Baseline results are abnormal Patient has symptoms of adverse reactions	Rifampin is contraindicated or should be used with caution in human immunodeficiency virus (HIV)-infected patients taking protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs) Decreases levels of many drugs (e.g., methadone, coumadin derivatives, glucocorticoids, hormonal contraceptives, estrogens, oral hypoglycemic agents, digitalis, anticonvulsants, dapsone, ketoconazole, and cyclosporin) Might permanently discolor soft contact lenses

Table 2.5 Medications to treat tuberculosis infection: Doses, toxicity, and monitoring requirements

Drug	Oral dose (mg/kg) (maximum dose)				Adverse reactions	Monitoring	Comments
	Daily		Twice weekly*				
	Adults	Children	Adults	Children			
Rifabutin	5 (300 mg)[§]	—	5 (300 mg)[§]	—	Rash Hepatitis Fever Thrombocytopenia Orange-colored body fluids (secretions, urine, tears) With increased levels of rifabutin Severe arthralgias Uveitis Leukopenia	Clinical monitoring at Weeks 2, 4, and 8 when pyrazinamide given Complete blood count, platelets, and liver function tests[†] at baseline in selected cases[‡] and repeat measurements if Baseline results are abnormal Patient has symptoms of adverse reactions Use adjusted daily dose of rifabutin and monitor for decreased antiretroviral activity and for rifabutin toxicity if rifabutin taken concurrently with PIs or NNRTIs[§]	Rifabutin is contraindicated for HIV-infected patients taking hard-gel saquinavir or delavirdine; caution is also advised if rifabutin is administered with soft-gel saquinavir Reduces levels of many drugs (e.g., PIs, NNTRIs, methadone, dapsone, ketoconazole, coumadin derivatives, hormonal contraceptive, digitalis, sulfonylureas, diazepam, ß-blockers, anticonvulsants, and theophylline) Might permanently discolor contact lenses
Pyrazinamide	15–20 (2.0 g)		50 (4.0 g)	—	Gastrointestinal upset Hepatitis Rash Arthralgias Gout (rare)	Clinical monitoring at Weeks 2, 4, and 8 Liver function tests[†] at baseline in selected cases[‡] and repeat measurements if Baseline results are abnormal Patient has symptoms of adverse reactions	Treat hyperuricemia only if patient has symptoms Might make glucose control more difficult in persons with diabetes Should be avoided in pregnancy but can be given after first trimester

* All intermittent dosing should be administered by directly observed therapy.

† AST or ALT and serum bilirubin.

‡ HIV infection, history of liver disease, alcoholism, and pregnancy.

§ If nelfinavir, indinavir, amprenavir, or ritonavir is administered with rifabutin, blood concentrations of these protease inhibitors decrease. Thus, the dose of rifabutin is reduced from 300 mg to 150 mg/d when used with nelfinavir, indinavir, or amprenavir; and to 150 mg (two or three times a week) when used with ritonavir. If efavirenz is administered with rifabutin, blood concentrations of rifabutin decrease. Thus, when rifabutin is used concurrently with efavirenz, the daily dose of rifabutin should be increased from 300 mg to 450 mg or 600 mg. Pharmacokinetic studies suggest that rifabutin might be given at usual doses with nevirapine. It is not currently known whether dose adjustment of rifabutin is required when used concurrently with soft-gel saquinavir. For patients receiving multiple PIs or a PI in combination with an NNRTI, drug interactions with rifabutin are likely more complex; in such situations, the use of rifabutin is not recommended until additional data are available.

2.13.4 Efficacy of PT in HIV infected individuals.

Several large randomized trials have shown the efficacy of PT in the prevention of the progression to active TB in HIV-infected persons (Table 2.6). Randomized trials administering isoniazid (H) for 6 months and 12 months duration have shown a significant decrease of TB incidence in PPD-positive persons compared to those who took placebo. IPT for PPD-positive persons living in areas with high TB prevalence will reduce the risk of developing active TB in short term to around 40% of what it would have been without such treatment [WHO/UNAIDS, 1999]. In PPD-negative persons, the efficacy of PT remains unproven. Some studies included all subjects regardless of PPD test result. The most recent meta-analysis of PT including these studies suggested that the effect of PT was restricted to PPD-positive persons [Bucher HC, et al, 1999].

Table 2.6 Randomized clinical trials of TB preventive in HIV infected persons

Author/Setting (year)	Regimen	TB Outcome	Comment
Pape/Haiti (1993)	H OD x 12 mo Placebo	2.2 per 100 py 7.5 per 100 py	All patients
Gordin/US (1997)	H OD x 6 mo Placebo	0.4 per 100 py 0.9 per 100 py	60% IDU Anergy cohort
Whalen/Uganda (1997)	H OD x 6 mo HR OD x 3 mo HRZ OD x 3 mo Placebo	1.1 per 100 py 1.3 per 100 py 1.7 per 100 py 3.4 per 100 py	PPD+ve clients 2 drug regimen showed more toxicity Anergy cohort H daily vs placebo: 3.06 per 100 py 2.53 per 100 py
Hawken/Kenya (1997)	H OD x 12 mo Placebo	5.6 per 100 py 8.0 per 100 py	PPD +ve, no significant difference
Halsey/Haiti (1998)	H biw x 6 mo RZ biw x 2 mo	1.7 per year 1.8 per year	Compliance better with RZ
Mwinga/Zambia (1998)	H biw x 6 mo RZ biw x 3 mo Placebo	4.94 per 100 py 4.65 per 100 py 8.06 per 100 py	All patients No effect on mortality
Gordin/US, Mexico, Haiti, Brazil (2000)	RZ OD x 2 mo H OD x 12 mo	0.8 per 100 py 1.1 per 100 py	PPD+ ve Adherence better with RZ

2.13.5 Treatment regimens of Latent Tuberculosis Infection in Thailand

National Recommendation Guideline of Thailand for prevention of Tuberculosis, they recommend this regimen: **INH 9 months 300 mg daily for HIV-infected person** [TB division, Ministry of Public Health, Thailand. 2001]

2.14 What is the process of treatment of Latent TB Infection?

2.14.1 Diagnosis of Latent Tuberculosis Infection

The tuberculin skin test is the only proven method for identifying infection with *M. tuberculosis* in persons who do not have TB disease. Although the available tuberculin skin-test antigens are <100% sensitive and specific for detection of infection with *M. tuberculosis*, no better diagnostic methods have yet been devised.

Different types of tuberculin tests are available, such as the **Mantoux tuberculin skin test** and the multiplepuncture test. The Mantoux tuberculin skin test is the preferred type because it is the most accurate. The Mantoux skin test is given by using a needle and syringe to inject 0.1 ml of 5 **tuberculin units** of liquid tuberculin between the layers of the skin (intradermally), usually on the forearm. A tuberculin unit is a standard strength of tuberculin. The tuberculin used in the Mantoux skin test is also known as **purified protein derivative**, or **PPD**. For this reason, the tuberculin skin test is sometimes called a **PPD skin test**. With the Mantoux skin test, the patient's arm is examined 48 to 72 hours after the tuberculin is injected. **Most people with TB**

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Table 2.7 Classifying the Tuberculin Skin Test Reaction

5 or more millimeters	**10 or more millimeters**	**15 or more millimeters**
An induration of **5 or more millimeters** is considered **positive** for # People with HIV infection # Close contacts # People who have had TB disease before # People who inject illicit drugs and whose HIV status is unknown	An induration of **10 or more millimeters** is considered **positive** for # Foreign-born persons # HIV-negative persons who inject illicit drugs # Low-income groups # People who live in residential facilities # People with certain medical conditions # Children younger than 4 years old # People in other groups as identified by local public health officials	An induration of **15 or more millimeters** is considered **positive** for # People with no risk factors for TB

Source: Self-study Modules on Tuberculosis , Centers for Disease Control and Prevention(CDC)

2.14.2 Screening for Tuberculosis disease

All people being considered for preventive therapy should receive a medical evaluation. One reason for this evaluation is to **exclude the possibility of TB disease**, because treating TB disease with a preventive therapy regimen (usually a single drug) can lead to drug resistance. To rule out the possibility of TB disease, clinicians should determine whether the patient has symptoms of TB disease, and they should evaluate the patient with a chest x-ray. People with symptoms of TB disease or chest x-ray findings suggestive of TB disease should be given treatment for TB disease, not TB infection.

Tuberculosis cases are classified as either pulmonary TB or extra-pulmonary TB. [WHO, 1997, Payanandana & kladphuang, 1999]

Pulmonary tuberculosis:

Patient with pulmonary tuberculosis are further sub-divided into smear-positive and smear-negative cases.

- Smear-positive pulmonary TB
  a) a patient with at least two sputum specimens positive for acid-fast bacilli by microscopy(AFB+ve) ;
  b) a patient with at least one AFB+ve and chest x-ray suggestive abnormalities consistent with pulmonary TB; and a decision by a physician to treat with a full curative course of anti-TB chemotherapy;
  c) a patient with at least one AFB+ve, which is culture positive for M. tuberculosis.

- Smear-negative pulmonary TB

  a) a patient with two AFB-ve, chest x-ray suggestive abnormalities consistent with extensive pulmonary TB(interstitial or miliary), and a decision by a physician to treat with a full curative course of anti-TB chemotherapy;

  b) a patient with AFB-ve and culture result is positive for M. tuberculosis.

Extra pulmonary tuberculosis:

TB of organ other than lung i.e. pleura, lymnode, abdominal viceras, skin, bone and joint, meninges, reproductive system, urinary system, miliary tuberculosis

a) a patient with AFB+ve or culture in one examination from extrapulmonary specimens

b) a patient with microbiological and clinical evidence of active TB and decision to give full treatment has been made by physician.

2.14.3 Monitor for adherence and toxicity of treatment of LTBI

Because persons with LTBI are not clinically ill and may not be motivated to undergo treatment, nonadherence occurs commonly in all steps of the treatment process. Patient should be monitored at the routine visits for adherence with treatment , drug toxicity, and signs or symptoms of active TB. Patients who interrupt therapy should be couselled about the reasons for stopping. Clients with symptoms of

tuberculosis or toxicity to medication should be evaluated immediately. Preventive therapy should not be continued if the patient develops signs or symptom of tuberculosis.

Adherence to treatment of LTBI is influenced by many factor such as out-migration for job search in other area, denial of HIV-infection status, perceived side effect of isoniazid and misunderstanding about duration of preventive therapy. [Ngamvithayapong et al. 1997] In additional, adherence is also influenced by the length of therapy, complexity of the regimen, and side effects of the medications. Adherence to treatment decreases with time, whereas the efficacy of the regimen increases with the length of therapy [IUATLD/WHO 1982] Patients may be more adherent to the 2-mo regimen of rifampin and pyrazinamide because of the shorter length of therapy; however, this regimen also involves taking multiple medications, and patients may not tolerate this regimen as well as isoniazid, thus potentially resulting in nonadherence.

Determinants of adherence to treatment of TB and LTBI are not well understood [Sumartojo et al. 1993.] For example, demographic factors are not reliable predictors of adherence. However, culturally influenced beliefs and attitudes may result in misinformation about TB and may adversely affect adherence [Carey et al.1997]

The main strategies that have been employed to promote adherence with treatment of LTBI are patient education [Morisky et al. 1990] ,the use of lay health workers from the patient's social and/or cultural group. [Sumartojo et al. 1993.] incentives (e.g., cash payments) [White et al. 1998] , and directly observed therapy (DOT) [Nolan et al. 1997]

2.14.4 Evaluation of outcome for treatment of latent tuberculosis infection

Programs or centers that offer treatment of latent tuberculosis infection should include attendance at scheduled appointments, completion rate (number of persons start started on treatment of latent tuberculosis infection and number completed), toxicity and withdraws from therapy due to toxicity, number of suspected TB cases in screening and monitoring of therapy. Individual records should be maintained to document use of treatment of latent tuberculosis infection. Individual information will be aggregated for regular reports, which may be used by the TB programme to estimate future drug requirements. In addition, evaluation of treatment of latent tuberculosis infection in term of health economic should be concern.

2.15 Why do we need economic evaluation for the treatment of latent tuberculosis infection?

"Is the treatment of latent tuberculosis infection cost-effective?" is still a question often overheard in debates concerning the provision of health service of Thailand.

Why should we concern about the cost or health economic? In the world of economists, resources – people, time, facilities, equipment, and knowledge- are scarce, so choices must and will always be made concerning their deployment. We want to spend the available funds in most effective fashion. Although it would be pleasant to practice in a world where economic constraints were not factors, none of use does. It is

in decision making by individual physicians about individual patients that the biomedical and economic considerations of clinical practice come together.

The economic analysis is one of tool that can be used to help us choose the most efficient health care program by considering its costs and consequences under the assumption that there is no change in equilibrium after the choice is made. It is crucial that the outcome must be meaningful enough to value it implicitly or preferably explicitly in order to make decision . However, other factors such as the ethical issue, political factors, must always come into play in the process of decision making.

The economic analyses share common feature in cost, but they often differ in the way they measure consequences.[Drummond et al. 1997] (See in table 2.8)

Table 2.8 Measurement of costs and consequences in economic evaluation

Types of study	Measurement /valuation of costs	Identification of consequences	Measurement /valuation of consequences
Cost-minization analysis	Baht	Identical in all relevant aspects	None
Cost-effectiveness analysis	Baht	Single effect of interest, common to both alternatives, but achieved to different degrees	Natural units
Cost-benefit analysis	Baht	Single or multiple effects, not necessarily common to both alternatives and common effects may be achieved to different degrees by the alternatives	Baht
Cost-utility analysis	Baht	Single or multiple effects, not necessarily common to both alternatives and common effects may be achieved to different degrees by the alternatives	Healthy days or (more often) quality-adjusted life-years

2.16 What are the costs and consequences in the economic evaluation of treatment of latent TB infection?

2.16.1 What are the costs?

Cost is defined as the value of resources used to produce something, including a specific health service or a set of services which may be expressed as a monetary or non-montery value of actual expenditure for the acquisition of these goods or services. [Crease and Parker, 1990]

Costs, positive or negative that are cost by an intervention and that would not have been incurred in the absence of the intervention, such as the cost of treating side effects of a medication and the cost of continuing to treat persons who live longer because of an intervention.

Classification of cost

Cost can be classified in two major economic categories:

1. **Direct cost**

The cost of the materials and labor that go directly into production of goods or service. Direct cost are essentially transactions. This transaction may be for the purchase of medical services as well as for non-medical services. Direct medical cost include labor cost of staff at hospital, drug, laboratory test, radiological procedures, hospitalization and also the cost for treatment of drug adverse that may be occur. Direct non-medical service such as transportation, accommodations, support homecare worker.

2. **Indirect cost**

The cost of lost productivity and monetary values, are essentially those of life and livelihood. They are the cost that are incurred because of morbidity and those that are incurred because of mortality which is premature. Additionally, including the cost occur from opportunity cost due to go to hospital that makes patient absence from work.

3. **Intangible cost**

The cost which are those of pain, suffering etc. associated with treatment.

While direct cost can often be measured in rather straight-forward fashion, indirect cost are more difficult to measure, and intangible costs are more even more so.

Whose costs should be considered? (Type of Viewpoint)

Costs, outcome, and benefits might be seen differently from the points of view of society,the patient, and the provider. The cost to the **provider** is the true cost of delivering the service, regardless of the charge. The cost to **the patient** is the amount the patient will need to pay for the service(that is, the portion not covered by insurance) plus the other costs that might be incurred because of the illness or the treatment. Including time missed from work. The cost to society is, in essence. The total net cost to all of the different components of society. The cost to **society** should be considered to be the opportunity cost to society. Which is determined by considering the

implication of the resources having been consumed and giving up the opportunity to use the resources for some other purpose.

The dimension of economic analysis (perspective) like a statue. Just as the cost, outcomes, and benefits may seem different from perspectives, so might a piece of sculpture look different depending on where you are standing around it.

2.16.2 How to measure the effectiveness?

Before go to measure of effectiveness, three steps in medical evaluation are needed to understand as this; .[Drummond et al. 1997, Ratanakul P., 1987]

1. Efficacy- Can it work?(under ideal condition)
2. Effectiveness- Does it work?(in the usual practice)
3. Efficiency- Is it reaching those w ho need it? Is it done economically?

Can it work ? Does the health programme do more good than harm to people who fully comply with the associated recommendations or treatments? This type of evaluation is concorned with **efficacy.**

Does it work? Does the health programme do more good than harm to those people to whom it is offered? This form of health care evaluation, which considers both the efficacy of a service and its acceptance by those to whom it is offered, is the evaluation of **effectiveness** or usefulness.

Is it reaching those who need it? Is the health program accessible to all people who could benefit from it? Evaluation of this type is concern with available or **efficiency.** Efficiency is a measure of the degree to which the resources that are expended result in a substantial beneficial outcome.

Effectiveness (Consequences or Outcome)

Because of the difficulty in capturing all the important outcomes of health programes in money term (How do you value life?), so the effectiveness measures is focused rather than "benefits". It is important to be sure that the effects you are measuring are the results of the resource inputs whose costs you also are calculating for each particular alternative.

These are 5 steps for measuring effectiveness: [Crease and Parker, 1990]

1. Choosing an indicator(measure) of effectiveness **(What to measure)**
2. Judging the merits of effectiveness measures.
    - Is the effectiveness measure comparable between alternatives?
    - Does the effectiveness measure have side-effects?
    - Is the measure sufficiently sensitive?
3. Measuring effectiveness: **(How to measure)**
4. Locating effectiveness data: Sources of information.
5. Expressing effectiveness measures. **(How to value)**

2.16.3 What is the Cost-effectiveness analysis?

Cost effectiveness analysis is a comparison of the cost different ways to achieve a common outcome. The result that we obtain is the cost per unit of outcome or the Unit of outcome per dollar spent. For example, a cost-effectiveness analysis may tell us the number of dollars spent per life saved from a treatment program. In this study cost-effectiveness analysis will tell that the number of dollars spent per 1 patient achieve treatment with completion.

Cost effectiveness analysis of treatment of LTBI mean that the number of dollars spent per achieve 1 patient with completed treatment.

2.16.4 What are the steps for Cost-effectiveness analysis?

There are five steps that are required for every cost-effectiveness analysis. Stated in terms of a program, they involve: [Creese and Parker 1990]

1. Defining the program's objective.
2. Identifying the alternative ways to achieve objective.
3. Identifying and measuring the costs of each alternative.
4. Identifying and measuring the costs of each alternative.
5. Calculate and interpret the cost-effectiveness of each alternative.
6. Incremental analysis

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